TITLE OF THE INVENTION:

THERAPEUTIC USES OF UVA

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional application 60/372,005 filed April 12, 2002.

BACKGROUND OF THE INVENTION

The present invention relates to the use of UVA irradiation, preferably UVA1, to enhance the effectiveness of the body's immunologic response against abnormal cells, infecting cells, infected cells, infectious agents, and other medically relevant targets.

The history of UVA treatment (normally radiation in the range 320 nm to 400 nm) against certain non-infectious diseases, in particular lupus erythematosus and scleroderma, which are autoimmune diseases, and eczema and mastocytosis, suggests that the result of UVA treatment is a diminishment of the immune response, for example, including a reduction in active immune cells.

An invention presented here is, nevertheless, the use of low levels of UVA to combat abnormal cells, such as papilloma virus-infected cells (as in warts), other types of precancerous cells, and cancerous cells.

Some success had been reported for the use of UVA radiation to prepare the body to fight a subsequent infection, that is, as a purely preventive approach. Nonetheless, such an approach is of nearly no utility, because it is not practical to treat large numbers of subjects who may or may not become subsequently exposed to an infectious agent. In

contrast, an invention presented here comprises the use of low levels of UVA to treat an existing infection and/or condition.

There have been efforts to develop creams and ointments for application onto the skin for the purpose of altering local expression of cytokines in the treatment of certain conditions. There is a need, however, to develop methods that provide better penetration and therefore better depth of effect. The current invention addresses these needs.

Furthermore, to facilitate the implementation of those and related inventions, a device that allows precise control of UVA radiation is disclosed, as is a device that allows convenient delivery of UVA radiation to internal sites, including but not limited to internal mucosa.

BRIEF SUMMARY OF THE INVENTION

Use of UVA with abnormal cells

In a first general aspect, the invention is a method for treating a condition characterized by the presence of abnormal cells in a person or animal, said method comprising the step of irradiating said abnormal cells and/or nearby tissue (within 5 cm of the perimeter of radiation) of the person or animal with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range, most preferably from part or all of the 340-400 nm range) at a tissue surface dose in the range 1 to 15 Joules/cm^2 within a 2-hour period (either by continuous or interrupted administration), wherein the condition is selected from the group consisting of a neoplastic condition, a proliferative condition, a precancerous lesion, a condition treated by an interferon or a compound or a procedure that induces an interferon, and a virus-caused condition.

It is understood that repeated administration (for example, 3 times per week for 2 weeks) of doses of 1 to 15 joules/cm^2 as described herein will be desirable for treatment.

Regarding that first general aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/cm^2;

2) the dose per unit time is in the range to deliver 5 J/cm^2 in 30 seconds to 30 minutes (*i.e.*, 1-60 min for 10 J/cm^2);

3) the surface area of tissue irradiated is at least 0.3 cm^2;

4) For warts, the surface area of tissue irradiated is not more than 50 cm^2;

5) the abnormal cell is in the path of irradiation; and

6) the abnormal cell is outside the perimeter of the path of irradiation but is within 5 cm of said perimeter; and

7) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Use of UVA with infections

In a second general aspect, the invention is a method for treating an infectious condition in a person, said method comprising the step of irradiating tissue of that person with UVA irradiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range, more preferably from all or part of the 340-400 nm range) at a tissue surface dose in the range 1 to 15 J/cm^2 (more preferably 1 to 7.5 J/cm^2, most preferably 1 to 5 J/cm^2) within a 2-hour period, wherein infecting cells are in the tissue.

Regarding that second general aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/cm^2;

2) the dose per unit time is in the range to deliver 5 J/cm^2 in 30 seconds to 30 minutes (*i.e.,* 45 sec to 45 min for 7.5 J/cm^2);

3) the surface area of tissue irradiated is at least 0.3 cm^2;

4) the surface area of tissue irradiated is not more than 50 cm^2

5) infected cells and/or an infectious agent is in the path of irradiation;

6) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Use of UVA with inflammatory conditions

In a third general aspect, the invention is a method of treating an inflammatory condition, said method comprising the step of irradiating such tissue of the person with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a tissue surface dose in the range 1 to 15 J/cm^2 within a 2-hour period.

Regarding this aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/cm^2;

2) the dose per unit time is in the range to deliver 5 J/cm^2 in 30 seconds to 30 minutes (*i.e.,* 1-60 min for 10 J/cm^2);

3) the surface area of tissue irradiated is at least 0.3 cm^2;

4) the inflamed area is in the path of irradiation;

5) the inflamed area is outside the perimeter of the path of irradiation but is within 5 cm of said perimeter;

6) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Use of UVA with vascular conditions

In a fourth general aspect, the invention is a method for treating a vascular condition, said method comprising the step of irradiating vascular tissue of the person with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a vascular tissue surface dose in the range 1 to 15 J/cm^2 within a 2-hour period. Regarding this aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/cm^2;

2) the dose per unit time is in the range to deliver 5 J/cm^2 in 30 seconds to 30 minutes (*i.e.,* 1-60 min for 10 J/cm^2);

3) the surface area of tissue irradiated is at least 0.3cm^2;

4) the surface area of tissue irradiated is not more than 50 cm^2;

5) the vascular condition is in the path of irradiation;

6) the vascular condition is outside the perimeter of the path of irradiation but is within 5 cm of said perimeter;

7) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Application to other animals

The inventions described herein are primarily intended for use with humans, but they can also be applied to other animals, including, but not limited to pets, farm animals, sport animals (*e.g.,* race horses and racing dogs), and other commercially and/or emotionally significant animals.

Device or system for regulating UVA radiation

In another general aspect, the invention is a device or system for regulating UVA radiation to a tissue, said device comprising:

(a) a source of UVA light; and

(b) a regulatory means; (and optionally)

(c) a UVA detector;

wherein the input to said regulatory means comprises a preset desired UVA dose/cm^2 and/or a preset desired UVA dose/cm^2/time; additional optional inputs to said regulator means include the distance from source to detector and distance from source to target treatment area, in situations when the source is mobile and the two distances may not be the same; and

wherein the output from said regulatory means is transmitted to the source of UVA light so as to achieve the desired UVA dose/cm^2 and/or preset desired UVA dose/cm^2/time.

In a preferred embodiment, the device (or system) permits the source of UVA light to be alternately directed at the UVA detector and a target area in or on a person. Direction at the UVA detector can be used to calibrate the light source and can be done before each use or, say, once a week or at other regular intervals. In a preferred embodiment for a device for irradiating a small target area, the device includes a mask to shield extraneous areas from radiation exposure, and said mask can incorporate a detector. In a preferred embodiment for a device irradiating a very large target area, such as whole-body surface irradiation (*e.g.,* a light box), a detector can be incorporated into a wall of said light box.

In a particular embodiment, the device permits the source of UVA light to be alternately directed at the UVA detector and a target area in or on a person.

Preferably the regulatory means comprises a computer chip.

In embodiments where the source of UVA light is adapted for insertion into an internal site, such as a mucosal-lined cavity, the cross-sectional diameter of said source (or the major axis of said source, if the cross-section is not circular in shape) being less than 8 cm, preferably less than 4 cm, and most preferably less than 3 cm. Preferably in such cases, the source of UV light has a circular or elliptical cross section, most preferably circular. In the case of a circular cross-section, the source may, for example, be cylindrical in shape. Generally, if the target is an internal site, the target and UVA source should not be more than 4 cm apart. In contrast, if the target is a surface site, the target and source can be up to 60 cm apart (as might, for example, occur inside a light box resembling a tanning box).

In particular embodiments, well-suited for insertion into mucosal cavities, the UV source is disposed within a shell, the shell comprising an aperture (air or UV-transmitting quartz, plastic, glass, or other UV-transmitting material) that permits UV light to be transmitted from the source to outside the shell.

In some particular dosage embodiments, the preset desired UVA dose/cm^2 is the dose within a distance of not more than 60 cm from an outer surface of the UVA source (or the outer surface of the shell surrounding the UVA source) and is in the range 1 to 15 J/cm^2. For internal applications, said distance is preferable not more than 4 cm. In the device or system the source of UVA light delivers light in the range from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range, and most preferably from part or all of the 340-400 nm range.

Reflecting the purpose of the device or system, the source of UVA light is disposed so that the irradiated tissue is neoplastic tissue, proliferative tissue, precancerous tissue, infected tissue, tissue with a condition that can be treated with an interferon or a compound or procedure that induces an interferon, and/or tissue containing a virus or viral genetic material. The device or system is well-suited for treatment of tissue that is a wart and/or infected with a virus that causes a wart.

It is clear that many of the embodiments described above represent features that can be combined with the features of one or more other embodiments.

As to all UVA or UVA1 radiation denoted herein, the radiation may be administered over the entire range of wavelengths or within a narrow band of wavelengths as created, for example, by a laser.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic view of a device of the invention.

Figure 2 is a schematic view of a device of the invention.

Figure 3 is a schematic view of a device of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Neoplastic conditions that are targets for the present invention include, but are not limited to, a skin cancer, a cancer of a mucous surface, a cancer of an epithelial surface, a melanoma, a basal cell cancer, a squamous cell cancer, a Kaposi's sarcoma, and an adenocarcinoma.

Proliferative conditions that are targets for the present invention include, a keloid, an actinic keratosis, a polyp, a hemangioma, and a condition treated by an interferon or a compound or procedure that induces an interferon.

Pre-cancerous lesions that are targets for the present invention include, but are not limited to, an actinic keratosis, a polyp, a condition treated by an interferon or a compound or procedure that induces an interferon, and a viral infection. Said viral infection includes, but it not limited to, a papilloma virus infection, a herpes virus infection, and a retroviral infection.

Virus-caused abnormal cell conditions that are targets for the present invention include, but are not limited to, warts (caused by papilloma virus), molluscum contagiosum (caused by a pox virus), Kaposi's sarcoma (caused by human herpes virus-8), herpes simplex (caused by human herpes viruses-1 and –2), herpes zoster (caused by the

varicella zoster virus), and a condition treated by an interferon or a compound or procedure that induces an interferon, by way of examples.

Warts include, but are not limited to, "verruca vulgaris", which is a term generally referring to lesions outside the groin, and "condyloma", which is a term generally referring to lesions in the groin area. Locations of warts can be anywhere on the skin (most commonly hands, feet, penis, and vulva), as well as mucous membranes including, but not limited to, the anus, the vulva, the vagina, the uterine cervix, and the mouth.

Infectious conditions that are targets for the present invention include, but are not limited to, leishmaniasis, a parasitic infection, an infection by an intracellular organism, a fungal infection, a granulomatous disease, herpes infection, a papilloma virus infection, a wart, a cytomegalovirus infection, a mycobacterial infection, an atypical mycobacterial infection, an MAI infection, a bacterial infection, a viral infection, a slow viral infection, a prion infection, a spirochete infection, Lyme disease, an HIV-related infection, a Kaposi's sarcoma, and an infection treated by an interferon or a compound or procedure that induces an interferon. As regards location, infectious conditions of particular interest are a cutaneous infection, an infection of a mucous membrane, a genital infection, an oral infection, an infection involving an epithelial surface (including, but not limited to, the gastrointestinal epithelium and the genitourinary epithelium), a nasal infection, a cervical infection, and a penile infection.

Leishmaniasis of particular interest is one selected from the group consisting of L. mexicana, L. major, L. donovani, L. amazonensis, a Leishmania species that infects humans, a leishmania species that causes cutaneous disease, a Leishmania species that causes visceral disease, and a Leishmania species that infects an animal.

Inflammatory conditions that are targets for the present invention include, but are not limited to, psoriasis, and an inflammatory bowel disease. Inflammatory bowel disease includes, but it not limited to, Crohn's disease and ulcerative colitis.

Vascular conditions that are targets for the present invention include, but are not limited to, hemangioma and a vascular condition associated with HIV infection.

It is expected that UVA (preferably all or part of the UVA1 range) will be useful in the treatment of any disease or condition where increasing IL-12, increasing IFN-γ, shifting from TH-2 to TH-1, and/or suppressing TNFα secretion would provide benefit.

It can be seen from the foregoing that the irradiated tissue may be skin or internal mucosal tissue, such as the gastrointestinal tract, the genitourinary tract, the respiratory tract, or internal organs.

UVA sources and detectors and intensity regulators

One of many commercially available UVA sources is the Berger Solar Simulator, which can for example be used with a 3-mm thick 345 mm Schott filter to get rid of UVB and UVA2, or used with window glass to get rid of UVB but not UVA2. Additionally, UVA fluorescent bulbs can be obtained from many companies. Lasers that generate wavelengths within the UVA or UVA1 ranges can also be used. Possible types of light sources also include fluorescent bulbs, fluorescent bulbs with filters, lasers, solid-state devices, and incandescent sources with filters.

For irradiation of internal organs or internal mucosal tissue, the UVA source can be at the tip of a rigid or flexible tube. Alternatively, a rigid or flexible waveguide or waveguides can be used to deliver light internally, while the source is external. Alternatively, a rigid tube, such as or similar to a uterine speculum or a rigid

sigmoidoscope, can allow access of light to a target area. Illustrative, but not limiting, examples include irradiation of mucosal tissue such as the uterine cervix, anus and/or sigmoid rectum in the treatment of conditions affecting those and nearby locations. An example of such a condition includes, but is not limited to, warts.

In further embodiments well-suited for insertion into mucosal cavities, the device incorporates a tube-like structure that conveys UVA radiation from a source (which would be connected to one end of the tube-like structure) to a target area or areas on or in the patient (and the radiation would come out of the other end of the tube-like structure). A waveguide (or conveyance) can be made that is capable of conveying UVA. A fiber-optic device (much like a colonoscope) is also contemplated, given that glass transmits UVA. Even a rigid tube, such as one resembling a sigmoidoscope or even a vaginal speculum, would work for areas that are only a short distance inside a bodily orifice (i.e., the same situations in which rigid sigmoidoscopes and speculums have been used). In addition, a rigid or flexible device that has the UVA source within it or even right at the end that is inserted into the patient is also contemplated. Emission of UVA from the end, or from the side of the UVA source, is contemplated. Also, a means to visualize the target area on or in the patient can also be incorporated, including but not limited to a fiber-optic device, such as an endoscope, and may include a visible light source. In this way, specific lesions are visualized, and can be specifically identified for radiation treatment.

Also envisioned is a wand that emits UVA from all around its sides (and optionally the tip as well), said UVA either conveyed from a radiation source external to the wand or generated within the wand. Said wand can be flexible or rigid. Said wand

can be attached to a flexible or rigid tube-like structure (such as one described in the preceding paragraph), or could be the entire portion of the device that is inserted into a bodily orifice of a patient. An advantage here is to reduce the amount of time spent irradiating the internal mucosa or organ by, in effect, dispensing with specific targeting of lesions. The wand can also incorporate a sheath, such as a sliding sheath, or a mask, that can be used to adjust the area and/or portion of the wand that is available to emit UVA. The sheath or mask can fit over the exterior of the wand. Alternatively, the sheath or mask can be internal to the wand (but still blocking the UVA), so that nothing becomes trapped between the outer surface of the wand and the sheath or mask. The sliding sheath can be selected from the group consisting of a sliding sheath that slides from the base of the wand up, a sliding sheath that slides from the tip of the wand down, a circumferential sheath or mask, and a sheath that has an aperture or apertures in it to allow emission from one side or one area of the wand. In certain circumstances, the tip of the wand can be opaque, so that UVA is emitted from the sides only.

Any of these devices can also incorporate a light meter. The light meter can be in and/or attached to the device, so that a reading can be taken during irradiation of a patient. Alternatively, the light meter can be external to the device. External light meters include, but are not limited to, a light meter in a holder, such as a shielded holder (to block out external sources of UV), into which the tube-like structure and/or wand can be set and/or inserted and then turned on, to allow calibration before a use. The devices can also be made from materials that endure sterilization and other cleaning procedures, including but not limited to autoclaving. Any of these devices can also incorporate a tool and/or component commonly included in an endoscope, such as a source of visible light (mentioned above), a means to transmit an image to the

operator of the device (mentioned in different words above), a means to rinse or otherwise clear or clean a site (such as a tube to transmit liquid, such as water or saline, to the target area; and/or a tube to aspirate rinsate other liquids from the target area), and a means to remove a piece of tissue, such as a biopsy. Any of these devices can also be used to deliver UVA1.

UV detectors that can be used to detect UVA light are also available from many companies. If the detector is sensitive to both UVA and UVB light, filters can be used to make it UVA specific (or UVA1 specific). The Solarmeter model 5.0 can be used. Ultralight also sells UV detectors.

Detectors measure the power output per unit area (*e.g.,* in units of mW/cm^2), which is a measure of intensity at a given distance from a source. From this number, one can calculate how long it will take to achieve a desired dose (one watt: one joule/second). Alternatively, a device for regulating UV radiation, described above, can be constructed to calculate this automatically.

The design of UVA regulators (including computerized ones) that take input as to desired intensities or amounts and also input as to actual intensities and time, are well within the skill of the art.

EXAMPLES

The Examples are intended to illustrate the invention rather than limit it.

Example 1 - A device of the invention

A device of the invention can be understood by reference to Figure 1. In Figure1, a single source of UVA irradiation **1** and **1'** is shown at two positions where it creates UVA radiation beams **3** and **3'** respectively. In its first position, the beam irradiates an area **9** on the sole of a foot **11**. Within the area **9** is a wart **13**. If the source of UVA irradiation is swiveled about the axis **15** to its second position, denoted by **1'**, the beam impinges on a UVA detector **19**. A rigid rod **5** can be used to position the foot and the detector, respectively, relative to the UVA source, thereby ensuring that the foot and the detector are at the same distance from the UVA source when they are irradiated. Equivalently, the detector can be the moving component, swinging on a rigid rod where the foot **11** is, and back again to its original position, again ensuring that the foot and the detector are at the same distance from the UVA source when they are irradiated.

The device in Figure 1 is for a UVA source with a well-defined cross section. The size of the cross section of the beam can be further controlled by interposing, between the UVA source and its targets (foot and detector), a barrier with two apertures of identical size that allow identical irradiation of the foot and the detector. Equivalently, the detector can be incorporated into the barrier itself, next to or nearby to a single aperture that allows UVA to reach the foot.

A UVA regulator **21** receives from a person, or other source, input as to the intensity and amount of radiation that is desired for the sole of the foot. The regulator also receives as input, from the detector **19**, data on the amount of radiation that reaches the detector when the UVA source is at **1'**. Based on the desired intensity and/or amount of radiation, it sends, as output to the UVA source, a signal that causes the UVA source to provide the

desired intensity and/or amount of radiation. When the UVA source is moved to position **1**, the intensity and amount (intensity x time) of radiation will be that desired. In a preferred embodiment, the intensity of the UVA source is kept fixed, and the regulator adjusts the time of exposure to achieve the desired dose (amount) of radiation.

The device therefore ensures that the correct radiation will be administered even if the UVA source's radiation intensity is different from that specified by the manufacturer. This is indeed a common circumstance, particularly because UVA sources change over their useful lifetime.

Although illustrated for the irradiation of an external (cutaneous) wart, the system clearly can be adapted to use for irradiation of other conditions, including ones involving internal organs or internal mucosal tissue.

Figure 1 is highly schematic, for example, as regards the shape and structure of the sources of UVA irradiation and the irradiated tissue.

Example 2 - A device of the invention adapted for the irradiation of internal mucosal tissue

Such a device can be understood by reference to the schematic illustration in Figure 2. The source **21** of UVA light is disposed within a circular shell (or sheath) **23**. Within the shell there is an aperture **31**, which allows UVA light **35** emitted by the source to pass through the shell and irradiate tissue **33**. The spatial relationship between the tissue and the UVA source is only one of many possibilities. One significant alternative is to have the UVA light emitted by the end **27** of the UVA light source **21**, and have it pass through the open end **37** of the shell **23**. The end of the shell denoted by **37** need not be completely open, it may be partially closed or even

completely closed, depending on how much UVA light should be emitted through it.

Figure 2 shows a means **29** for setting the intensity of radiation (and therefore the dose per square meter of tissue per unit time). The means **29** is connected to the UVA light source **21** by an electrical conducting line **25**. A filter (not shown) to select only the desired wavelengths may be interposed between the UVA source and the tissue.

In Figure 2, the UVA source and the shell are both cylindrical although, because of the perspective of the schematic drawing, they may appear to have elliptical cross-sections. Nevertheless, elliptical and other cross-sections are also contemplated.

Figure 3 shows a variation of the device shown in Figure 2. In Figure 3, the UVA light **35** is emitted at the end **27** of the UVA light source.

Figures 2 and 3 are highly schematic. In Figure 3, for example, the light source **21** can represent a lamp, a lamp in combination with a fiber optic tube that ends at end **27** of the source, or simply a fiber optic tube connected to a lamp not shown in the figure. Also the source may not extend all the way along the shell (or sheath) **23**, but may be recessed within it. Alternately, the UVA source **21** may extend past the end of the sheath nearest the tissue and protrude from the sheath. Furthermore, in both Figures, the shapes of the UVA source and the sheath may differ considerably from that shown. For example, in many cases, it will be desirable to have those items long and thin, as for a wand or colonoscope.

Example 3 - Treatment of warts

A person with a cutaneous wart is treated. The wart is irradiated with UVA light

in the range 340 nm to 400 nm, created by passing light from a standard UVA fluorescent bulb (such as one would find in a PUVA box, available for example from Ultralite Enterprises, Inc., of Lawrenceville, GA, sometimes called UVA phototherapy chambers) through an acrylic filter that eliminates UVA2 and any UVB, but allowing UVA1 to pass. The intensity of the light at the surface of the wart is 5 mW/cm^2. The wart is exposed to the UVA1 light for 20 minutes (for a dose during that treatment of 5 mW/cm^2 times 1200 seconds, equals 6 J/cm^2). That treatment is repeated at intervals of 4 to 7 days, up until 12 treatments, unless the wart has disappeared or substantially shrunk prior to that number of treatments, in which case the course of treatments is terminated.

Exemplary treatments are similar for other conditions and disorders listed herein, including, but not limited to, actinic keratosis, keloid, a neoplastic condition, and/or an infectious conditions.